

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number
WO 01/11963 A1

(51) International Patent Classification⁷: **A01N 43/22**,
A61K 31/71 // (A01N 43/22, 25:34, 25:00)

(21) International Application Number: PCT/US00/19557

(22) International Filing Date: 2 August 2000 (02.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/148,618 12 August 1999 (12.08.1999) US

(71) Applicant (for all designated States except US): **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **SNYDER, Daniel, Earl** [US/US]; 7348 Yorkshire Boulevard, Indianapolis, IN 46229 (US).

(74) Agents: **DEMETER, John, C.** et al.; Eli Lilly And Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- With amended claims.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/11963 A1

EV 630723785 US

Entry into National Phase of PCT/EP2004/052762

Attorney Docket: I-2003.019 US

(54) Title: ORAL TREATMENT OF COMPANION ANIMALS WITH ECTOPARASITICIDAL SPINOSYNS

(57) Abstract: The invention provides single-dose oral formulations for controlling an ectoparasite infestation on a companion animal for a prolonged time, said formulations comprising a spinosyn component, or a physiologically acceptable derivative or salt thereof, and a carrier in oral dosage form. It also provides methods for controlling such infestations comprising orally administering a single dose of these formulations to the animal.

ORAL TREATMENT OF COMPANION ANIMALS WITH ECTOPARASITICIDAL SPINOSYNS

Companion animals, including but not limited to dogs, cats, and horses, are an increasingly important part of today's society. They provide pleasure and companionship to human friends, which leads to what has been termed the human-animal bond. Unfortunately, a number of insect pests and parasites can infest or infect these animals. Such pests include, for example, fleas, lice, mosquitoes, mites, ticks and certain fly species. Safe, effective ways to eliminate these pests are desired, both for the animal's well-being and for the comfort of its human associate.

The most common ectoparasites of cats and dogs world-wide are the cat and dog fleas, *Ctenocephalides felis felis* and *Ctenocephalides canis*, respectively. Interestingly, the cat flea very commonly infests dogs. Fleas annoy the animal it infests and the pet's owner. Frequently, fleas cause more serious problems by inducing flea-allergy dermatitis. It has been estimated that flea-related diseases account for over 50% of the dermatological cases reported to veterinarians [D. E. Bevier-Tournay, "Flea and Flea Control" *Curr. Vet. Therapy* 10: 586-592 (1989)]. In addition, the cat flea is known to transmit tapeworms in dogs and has been implicated in the transmission of cat scratch disease and murine typhus. Other pests of companion animals, such as ticks and mosquitoes, are also known to transmit disease. For example, ticks are known to transmit bacterial and viral diseases; and mosquitoes can infect dogs and cats with the filarial nematode that causes heartworm disease.

Furthermore, economic expenses involved in flea control are high. In the United States, for example, pet owners spend over \$1 billion dollars for flea

-2-

control products annually [R. Conniff, "When It Comes to Pesky Flea, Ignorance is Bliss," *Smithsonian*: 26: 76-85 (1995)].

Treatments currently available achieve varying degrees of success.

Most treatments involve chemicals applied to indoor and outdoor surfaces, as well as
5 to the pet. The chemicals used include a variety of carbamates, organophosphates,
pyrethrins and pyrethroids. These compounds often have toxic side effects that are a
problem for both the pet and its owner. For example, concentrated forms of
pyrethroids available for use on dogs are extremely toxic and lethal to cats and thus
cannot and should not be used on cats. In addition, there is evidence that the use of
10 these chemicals has led to multiple category insecticide resistance [N. K. Rust and M.
W. Dryden, *Ann. Rev. Entomol.* 42: 451-473 (1997)]. Thus, there continues to be a
need for relatively safe, effective agents for controlling ectoparasites on companion
animals, such as cat and dog fleas.

The spinosyns (also known as A83453 factors) are agricultural
15 insecticides that have shown activity against southern armyworm and other insects in
the order *Lepidoptera*, and cotton aphid and other members of the order *Homoptera*.
(See, for example, U.S. Patent No. 5,571,901).

The spinosyns were also known to have some ectoparasiticial activity,
i.e., they had *in vitro* activity against mosquito larvae, black blowfly larvae and adult
20 stable flies, which are members of the insect order *Diptera*, and transient systemic
activity against larval blowfly and adult stable fly in guinea pigs and sheep (see U.S.
Patent No. 5,571,901, col 26-32). Although it was suggested that the spinosyns
would be active against a number of ectoparasites in a number of animals by a variety

-3-

of routes, there have been no subsequently reported studies to support these suggestions.

This invention came about by the discovery that spinosyns, such as spinosyn A, can provide prolonged residual control of an ectoparasite infestation on a companion animal when a single dose of a spinosyn is administered orally to the animal. Thus, the invention provides a method for prolonged control of the ectoparasite in a safer manner than that achieved with previously known treatments.

In one aspect, this invention relates to a long-acting, single-dose oral formulation for controlling an ectoparasite infestation on a companion animal, said formulation comprising an ectoparasiticial amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier, in an oral dosage form.

In another aspect the invention relates to the use of a single, long-acting oral formulation of a spinosyn, or a physiologically acceptable derivative or salt thereof, for controlling an ectoparasite infestation on a companion animal.

It also relates to the use of a spinosyn, or a physiologically acceptable derivative or salt thereof, for the manufacture of a long-acting single-dose oral medicament for controlling an ectoparasite infestation on a companion animal.

This invention also relates to a method of controlling an ectoparasite infestation on a companion animal for a prolonged time, comprising orally administering a single dose of an effective amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, to the animal. An especially useful method of this invention is a method for controlling cat or dog fleas on a companion animal for a

-4-

prolonged time comprising orally administering a single dose of an effective amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, to the animal.

The invention further relates to an article of manufacture, comprising packaging material and a formulation for controlling an ectoparasite infestation on a companion animal contained within said packaging material, wherein said
5 formulation comprises

an oral long-acting unit dose of an ectoparasiticide amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier; and

10 wherein said packaging material comprises a label or package insert with instructions for orally administering the dose to the animal.

This article of manufacture or kit is particularly appropriate when the companion animal is a dog or a cat. When the animal is a dog, the formulation contained in the packaging material will generally be in tablet form, and the label or
15 package insert will indicate the number of tablets to be given by mouth to the dog and the timing of such administration. The timing of doses will generally be every 30 days. When the animal is a cat, the formulation contained in the packaging material will generally be a liquid formulation and the label or package insert will indicate the unit dose to be given by mouth to the cat. The timing of doses will generally be every
20 30 days. The contents of each kit would typically be sufficient to control the ectoparasite infestation for a period of several months.

Spinosyns are naturally derived fermentation products. They are macrolides produced by cultivation of *Saccharopolyspora spinosa*. The fermentation produces many factors, including spinosyn A and spinosyn D (also called A83543A

-5-

and A8354D). Spinosyn A and spinosyn D are the two spinosyns that are most active as insecticides. A product comprised mainly of these two spinosyns is available commercially under the trade name "spinosad". The major spinosyn factor, spinosyn A, is known to have an excellent human and animal safety and toxicological profile.

5 Each spinosyn has a 12-membered macrocyclic ring that is part of an unusual tetracyclic ring system to which two different sugars are attached, the amino-sugar forosamine and the neutral sugar 2N,3N,4N-(tri-O-methyl)rhamnose. This unique structure sets the spinosyns apart from other macrocyclic compounds.

Spinosyn A was the first spinosyn isolated and identified from the
10 fermentation broth of *Saccharopolyspora spinosa*. Subsequent examination of the fermentation broth revealed that *S. spinosa* produced a number of spinosyns that have been called spinosyns A to J (A83543A to J). The primary components are spinosyns A and D. Additional spinosyns, lettered from K to W, have been identified from mutant strains of *S. spinosa*. The various spinosyns are characterized by differences in
15 the substitution patterns on the amino group of the forosamine, at selected sites on the tetracyclic ring system and on the 2N,3N,4N-(tri-O-methyl)rhamnose group.

The term "spinosyn or a derivative thereof" as used herein refers to an individual spinosyn factor (spinosyn A, B, C, D, E, F, G, H, J, K, L, M, N, O, P, Q, R, S, T, U, V, W or Y), an N-demethyl derivative of an individual spinosyn factor, or a
20 combination thereof. For convenience, the term "spinosyn component" will also be used herein to mean an individual spinosyn, or a physiologically acceptable derivative or salt thereof, or a combination thereof.

Boeck et al. described spinosyns A-H and J (which they called A83543 factors A, B, C, D, E, F, G, H and J), and salts thereof, in U.S. Patent Nos. 5,362,634

-6-

(issued Nov. 8, 1994); 5,496,932 (issued March 5, 1996); and 5,571,901 (issued Nov. 5, 1996). Mynderse et al. described spinosyns L-N (which they called A83543 factors L, M and N), their N-demethyl derivatives, and salts thereof, in U.S. Patent No. 5,202,242 (issued Apr. 13, 1993); and Turner et al. described spinosyns Q-T (which they called A83543 factors Q, R, S and T), their N-demethyl derivatives, and salts thereof, in U.S. Patent Nos. 5,591,606 (issued January 7, 1997) and 5,631,155 (issued May 29, 1997). Spinosyns K, O, P, U, V, W and Y are described, for example, by Carl V. DeAmicis, James E. Dripps, Chris J. Hatton and Laura I. Karr in American Chemical Society's Symposium Series: Phytochemicals for Pest Control, Chapter 11, "Physical and Biological Properties of Spinosyns: Novel Macrolide Pest-Control Agents from Fermentation", pages 146-154 (1997).

The spinosyns can react to form salts that are also useful in the methods and formulations of this invention. The salts are prepared using standard procedures for salt preparation. For example, spinosyn A can be neutralized with an appropriate acid to form an acid addition salt. The acid addition salts of spinosyns are particularly useful. Representative suitable acid addition salts include salts formed by reaction with either an organic or inorganic acid such as, for example, sulfuric, hydrochloric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, cholic, pamoic, mucic, glutamic, camphoric, glutaric, glycolic, phthalic, tartaric, formic, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic and like acids.

Using oral formulations of spinosyns to systemically control ectoparasites of companion animals, as a single treatment modality or in combination with other commonly used ectoparasitocidal compounds, has several advantages.

-7-

Spinosad is a naturally derived fermentation product with an excellent human and animal safety profile, which is in contrast to currently used synthetic organically derived compounds such as synthetic organophosphates, pyrethroids and pyrethrins, organochlorines, and carbamates. For example, some of the currently used products
5 such as organophosphates and synthetic pyrethroids are very toxic to cats and can be lethal.

Spinosyns also provide advantages because they are very effective against fleas, mites, ticks, lice and flies with post-treatment residual protection, depending on the dosages used. Furthermore, spinosyns have no cross-resistance to
10 existing compounds. Thus, they are especially useful against parasite populations on companion animals that have existing levels of resistance to currently used products. Spinosyns, therefore, can be used in integrated pest management (IPM) programs to extend the life line of commonly used products where resistance is not well developed or has not yet developed.

15 Systemic efficacy (ingestion of blood containing spinosad by the blood feeding parasites, such as fleas) provides different mode of exposure compared to topically applied ectoparasiticides where contact with the parasite at the skin surface is the mode of exposure. The advantages of oral systemic treatments and killing of parasites from ingestion of blood, compared to topical applications and contact
20 killing, include:

- a) reduced exposure to the human applicator and children and objects in the animal's environment (e.g., flooring, carpets, furniture);
- b) no worry about loss from exposure of the animal to water
25 (lakes, streams, bathing, etc.) or from loss due to rubbing;
- c) no concern about UV exposure and degradation;

-8-

d) no problems with oxidation from oils on skin, etc.; and

e) assurance that the entire dose is administered (compared to a topical application where some of the dose may drip off, rub off and/or remain in the dispensing tube immediately after treatment).

5

The formulations of this invention may further include, in combination with the spinosyn component, one or more other compounds that have activity against the specific ectoparasite or endoparasite to be controlled, such as, for example, synthetic pyrethroids, natural pyrethins, organophosphates, organochlorines, carbamates, foramidines, avermectins, milbemycins, insect growth regulators (including chitin synthesis inhibitors, juvenile hormone analogs, and juvenile hormones), nitromethylenes, pyridines and pyrazoles.

10

All ratios, percentages, and parts discussed herein are "by weight" unless otherwise specified.

15

The term "oral formulation" means that the spinosyn component or components, either alone or in combination with one or more of the other types of compounds listed supra, is formulated into a product or formulation suitable for administering to the animal by mouth. These products or formulations include, but are not limited to, tablets, capsules, liquids, gels, pastes, oral sprays, buccal formulations, powders and chewable treats or animal feeds containing the active component or components. Generally, such formulations include a physiologically acceptable carrier. Such carriers are well known in the veterinary arts. Animal feeds are particularly useful carriers.

20

The term "controlling an ectoparasite infestation" refers to preventing, minimizing or eliminating an infestation by an ectoparasite. The term "ectoparasite"

25

refers to insect and acarine pests that commonly infest or infect companion animals.

Examples of such ectoparasites include the egg, larval, pupal, nymphal and adult stages of fleas, lice, mosquitoes, mites, ticks and blood-sucking, biting or nuisance fly species.

5 The term "companion animals" includes dogs, cats, horses, rabbits and other pets owned and maintained in close association with humans as part of the human-animal bond.

 The term "single-dose formulation" means that one dose of the formulation effectively controls the ectoparasite infestation for a prolonged time. The
10 term "prolonged time" comprises a period of at least 7 days, preferably a period of at least two weeks. The term "long-acting" means that the activity lasts for a prolonged time.

 The methods of this invention are carried out by orally administering the spinosyn component to the companion animal. Oral administration may be
15 carried out using tablets and animal feeds. For some animals, such as certain cats, administration is best accomplished by using an acceptable liquid formulation that is administered directly or added to their food ration. Especially useful methods of orally administering the spinosyn component are by administering it in chewable tablets or treats and animal feeds.

20 Conventional oral tablets generally consist of the spinosyn component, a diluent to assist in increasing the powder mass to a convenient size and improve compressibility, a binder to hold the compressed powder together and a lubricant to assist in densification and ejection from the tablet die. They may also contain a disintegrate to improve disintegration and dissolution as well as stabilizers, colors and

-10-

flavors. Tablets are often coated to improve appearance or taste or to alter the dissolution properties. Tablets can be designed to dissolve fast or slow, and depending on the actual volume and compressibility of the drug, large or small. They can be made chewable or to dissolve under the tongue or in the pouch of the cheek.

5 Conventional liquid formulations for oral administration are usually solutions, suspension or emulsions of the spinosyn component together with suitable diluents, solvents, flavors and colors to make a palatable dosage form. Other materials to complex, adjust pH, and improve mouth feel are also often used.

10 In carrying out the methods of this invention, an effective amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, is administered orally to the companion animal. The terms "effective amount" and "ectoparasitidal amount" refer to the amount needed to control the particular ectoparasite infestation. As those in the art will understand, this amount will vary depending upon a number of factors. These factors include, for example, the type of companion animal being
15 treated, its weight and general physical condition and the type of ectoparasite to be controlled.

20 In general, an effective amount refers to a dose of from about 1 to about 100 mg of the spinosyn/kg of body weight of the companion animal. More commonly, the effective amount is from about 10 to about 50 mg/kg of body weight of the animal.

 Tablet formulations will typically contain from about 1 to about 75 percent of spinosyn component or components (by weight) in the tablet. Animal feeds will typically contain from about 0.1 to about 10 percent of spinosyn component or components (by weight) in the feed.

The following examples illustrate the methods of this invention:

EXAMPLE 1

**Efficacy of Spinosad Administered *per os* to Dogs
for the Treatment and Control of *Ctenocephalides felis***

5

Methods: Nine random-source dogs of both sexes and various ages were used in this study. The dogs were housed individually in concrete-floored chain-link runs during the study period and were fed a commercial dry dog food ration with *ad libitum* access to water. The dogs were allocated to each of the 3 treatment groups (3 dogs per group) based on their pre-treatment flea counts from experimental infestations.

Each dog received one or more gelatin capsules containing technical active spinosad powder by mouth. They were dosed at either 50 or 100 mg/kg body weight on day 0. Each dog was fed approximately one-half can of moist dog food just prior to and just after receiving their individual doses. Each dog was experimentally infested with ~ 100 unfed adult fleas on test days -1, 0, 6, 13, 20, 27, 34, 41, and 48. Comb counts for live adult fleas were conducted ~24 hours following each of the subsequent experimental infestations, i.e., on test days 0 (8 hours post-treatment), 1, 7, 14, 21, 28, 35, 42 and 49.

Results: Geometric Mean Percent reduction in live adult flea counts compared to untreated control group in dogs treated orally with spinosad are listed below in Table 1.

-12-

Table 1: Geometric Mean Percent Reduction in Live Adult Flea Counts in Dogs Treated With Spinosad Compared to Untreated Control Group

Dose of Spinosad	Days Post-treatment								
	8hrs	D1	D7	D14	D21	D28	D35	D42	D49
50 mg/kg	97.4	100	99.3	99.7	99.5	95.0	78.1	69.9	ND ^a
100 mg/kg	98.9	100	100	100	99.5	99.7	99.4	97.5	94.

^a ND: not determined

No adverse reactions were seen.

EXAMPLE 2

Efficacy of Spinosad Administered *per os* to Dogs for the Treatment and Control of Brown Dog Ticks (*Rhipicephalus sanguineus*) and Cat Fleas (*Ctenocephalides felis*)

Methods: Twelve random-source dogs of both sexes and various ages were used in the study. The dogs were housed, fed, and watered as in Example 1. The dogs were allocated to each of the 3 treatment groups (4 dogs per group) based on their pre-treatment tick counts from experimental infestations. Each dog received by mouth one or more gelatin capsules containing either nothing (control) or technical active spinosad powder. The spinosad-treated groups were dosed at either 50 or 100 mg/kg body weight on day 0. Each dog was fed approximately one-half can of moist dog food just prior to and just after receiving their individual capsules. Each dog was infested with ~50 unfed adult ticks on test days -1, 7, 14, 21 and 28. Each dog was also concurrently infested with ~100 unfed adult fleas on test days -1, 7, 14, 21, 28, 35 and 42. Comb counts for live adult fleas and ticks were conducted ~48 hours following each of the experimental infestations (i.e., on test day 1) and on post-

-13-

treatment days 9, 16, 23 and 30 for both ticks and fleas and additionally on days 37 and 44 (for fleas only).

Results: Geometric Mean Percent reduction in live adult flea counts compared to untreated control group in dogs treated orally with spinosad are listed below in

5 Table 2.

Table 2. Geometric Mean Percent Reduction in Live Adult Flea Counts in Dogs Treated with Spinosad Compared to Untreated Control Group

10

	Days Post-treatment						
Dose of Spinosad	1	9	16	23	30	37	44
50 mg/kg	100	100	99.75	98.3	92.5	93.6	63.1
100 mg/kg	100	100	100	100	100	98.9	97.3

15

Geometric Mean Percent reductions in live adult tick counts compared to untreated control group in dogs treated orally with spinosad are listed in Table 3.

Table 3: Geometric Mean Percent Reduction in Live Adult Tick Counts in Dogs Treated with Spinosad Compared to Untreated Control Group

20

25

	Days Post-treatment				
Dose of Spinosad	1	9	16	23	30
50 mg/kg	94.8	67.8	49.1	52.1	5.0
100 mg/kg	97.2	91.5	70.6	79.7	71.3

Summary of Results (both examples): Orally administered spinosad was able to provide excellent immediate knockdown and long term post-treatment residual control of fleas on dogs. The 50 mg/kg dose provided greater than 90% flea efficacy

-14-

through day 37 of the study. The 100 mg/kg dose provided greater than 90% flea efficacy through day 49 of the study (when the study was terminated).

Orally administered spinosad also was able to provide excellent immediate knockdown and a moderate length of post-treatment residual control of ticks on dogs. The 50 mg/kg dose provided greater than 90% tick efficacy through day 1 of the study. The 100 mg/kg dose provided greater than 90% tick efficacy through day 9 of the study.

EXAMPLE 3

Efficacy of Spinosad Administered *per os* to Dogs for the Treatment and Control of Fleas (*Ctenocephalides felis*)

Methods: Thirty-two (32) random source dogs of both sexes and various ages were used in the study to evaluate different dosages and physical forms of spinosad and their impact on oral efficacy against fleas. The dogs were housed individually in concrete-floored chain-link runs during the study period and were fed a commercial dry dog food ration with *ad libitum* access to water. The dogs were allocated to each of the 8 treatment groups (4 dogs per group) based on their pre-treatment flea counts from experimental infestations. Each dog received by mouth one or more gelatin capsules containing technical spinosad in the different physical forms and dosages listed infra. They were dosed based on body weight on day 0. Each dog was fed approximately one-half can of moist dog food just prior to, and just after, receiving their individual gelatin capsules containing the specific spinosad formulation and dosage. Each dog was experimentally infested with ~100 unfed adult fleas on test days -1, 2, 6, 9, 13, 20, 27 and 34. Comb counts for live adult fleas were conducted

-15-

~24 hours following dosing or each of the subsequent experimental infestations (i.e.- test days 1, 3, 7, 10, 14, 21, 28 and 35).

Treatments:

5	Treatment No.	Oral Dose (mg/kg)	Formulation Type & Concentration
	1	11.25	Milled spinosad, technical, in gelatin capsules
	2	22.5	Milled spinosad, technical, in gelatin capsules
	3	45	Milled spinosad, technical, in gelatin capsules
	4	22.5	Amorphous spinosad, technical, in gelatin capsules
10	5	22.5	Unmilled spinosad, technical, in gelatin capsules
	6	Untreated control	None

Table 4 summarizes the results of this study.

15 **Table 4: Geometric Mean Percent Reduction in Live Adult Flea Counts Compared to Untreated Control Group in Dogs Treated Orally with Spinosad**

20	Treatment No.	Days Post-Treatment							
		1	3	7	10	14	21	28	35
	1	100.0	99.6	94.4	96.0	87.0	74.7	71.4	31.8
	2	100.0	100.0	100.0	99.6	99.0	91.9	78.5	50.95
	3	100.0	100.0	100.0	100.0	99.8	99.5	98.9	94.2
	4	100.0	100.0	100.0	100.0	100.0	97.8	91.4	56.1
25	5	100.0	100.0	100.0	100.0	100.0	99.3	98.9	60.4

Summary: Orally administered spinosad provided excellent immediate knockdown efficacy (99.6 to 100% on days 1 & 3 post-treatment) and also good-to-

-16-

excellent long term post-treatment residual control of fleas on dogs. The 45 mg/kg milled spinosad dose provided greater than 94% flea efficacy through day 35 of the study. The lower dosages of milled spinosad provided shorter post-treatment residual control based on the dose. The adult flea efficacy of the 22.5 mg/kg spinosad dosages of milled (mean particle size of ~ 5 microns), amorphous (non-crystalline), and unmilled (mixture of particles sizes greater than 5 microns with a distribution of up to ~ 200 microns) were similar and not statistically different at day 28 post-treatment, indicating that particle size or crystalline form does not impact the oral flea efficacy.

No adverse reactions were seen.

10

EXAMPLE 4

Efficacy of Spinosad Administered *per os* to Cats for the Treatment and Control of Fleas (*Ctenocephalides felis*)

15 **Methods:** Sixteen cats of both sexes and various ages were used in the study. The cats were housed individually in cages with litter boxes and were fed a commercial dry cat food ration with *ad libitum* access to water. The cats were allocated to each of the 4 treatment groups (4 cats per group) based on their pre-treatment flea counts from experimental infestations. Each cat received by mouth one or two gelatin capsules containing milled technical spinosad powder and were dosed at either 0, 12.5, 25 or 50 mg of spinosad per kg of body weight on day 0. Each cat was fed a small amount of moist cat food just prior to and just after receiving their individual gelatin capsules containing spinosad. Each cat was experimentally infested with ~100 unfed adult fleas on test days -1, 0 (8 hours), 2, 6, 9, 13, 20 and 27. Comb counts for live adult fleas were conducted ~24 hours following dosing or each of the

20

25

-17-

subsequent experimental infestations (i.e.-test days 0 @ 8 hours, 1, 3, 7, 10, 14, 21, and 28).

Table 5 summarizes the results of this study.

Table 5: Geometric Mean Percent Reduction in Live Adult Flea Counts Compared to Untreated Control Group in Cats Treated Orally with Spinosad

Spinosad, Oral Dose (mg/kg)	Hours/Days Post Treatment							
	8 hrs.	1	3	7	10	14	21	28
12.5	94.6	100	100	96.7	85.0	92.2	68.2	36.1
25	97.4	100	100	98.1	97.1	95.4	83.1	69.7
50	97.0	100	100	97.5	97.8	97.9	90.9	74.4

Summary: Orally administered spinosad provided excellent immediate knockdown efficacy (94.6 to 100% at 8 hours and on days 1 & 3 post-treatment) and also good to excellent long term post-treatment residual control of fleas on cats. The 50 mg/kg milled spinosad oral dose provided greater than 90% flea efficacy through day 21 of the study. The lower dosages of milled spinosad provided shorter post-treatment residual control based on the dose.

Adverse reactions: one cat in the 25 mg/kg dose group and 2 cats in the 50 mg/kg dose group vomited a small amount of food ~ 1 hour post-treatment. The cause is unknown.

EXAMPLE 5

The following is an example of a suitable tablet formulation:

	Component	Percent of Formulation by Weight
	Spinosad, technical, (90%)	5.5
5	Microcrystalline cellulose	20.0
	Compressible sugar	30.0
	Carboxymethyl cellulose, sodium salt, crosslinked	10.0
	Magnesium stearate	10.0
10	Silicon dioxide, colloidal	20.0
	Tuna (fish) flavoring	4.5
		100.0

Each tablet contains 5% of the spinosyn component by weight.

15

EXAMPLE 6

The following is an example of a suitable liquid formulation:

	Component	Percent of Formulation by Weight
	Spinosad, technical, (90%)	5.5
20	Water soluble dye	1.0
	Methyl cellulose	6.0
	Water	83.0
	Fish flavoring agent	4.5
		100.0

25

This formulation contains 5% of the spinosyn component by weight.

CLAIMS

1. A long-acting single-dose oral formulation for controlling an ectoparasite infestation on a companion animal, said formulation comprising an ectoparasitocidal amount of a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier, in an oral dosage form.
2. A formulation of Claim 1 wherein the spinosyn is spinosyn A.
3. A formulation of Claim 1 or 2 wherein the dosage form is a tablet and the amount of spinosyn is from 1 to 75 percent by weight of the tablet.
4. A formulation of Claim 1 or 2 wherein the dosage form is an animal feed and the spinosyn comprises from 0.1 to 10 percent by weight of the feed.
5. A formulation of Claim 1, 2, 3 or 4 wherein the animal is a dog, a cat, a horse or a rabbit.
6. A formulation of Claim 1, 2, 3, 4 or 5 wherein the ectoparasite is a cat flea, a dog flea, a biting fly, a nuisance fly, a mosquito, a tick or a louse.
7. An article of manufacture, comprising packaging material and a formulation for controlling an ectoparasite infestation on a companion animal contained within said packaging material, wherein said formulation comprises a long-acting oral unit dose of a formulation of Claim 1, 2, 3, 4, 5 or 6; and wherein said packaging material comprises a label or package insert with instructions for orally administering the dose to the animal.

-20-

8. The use of a spinosyn, or a physiologically acceptable derivative or salt thereof, for the manufacture of a long-acting single-dose oral medicament for controlling an ectoparasite infestation on a companion animal.

9. A use of Claim 8 wherein the spinosyn is spinosyn A.

5 10. A use of Claim 8 or 9 wherein the animal is a dog, a cat, or a horse.

11. The use of a single, long-acting oral formulation of a spinosyn, or a physiologically acceptable derivative or salt thereof, for controlling an ectoparasite infestation on a companion animal.

10 12. A use of Claim 11 wherein the spinosyn is spinosyn A.

13. A use of Claim 11 or 12 wherein the animal is a dog, a cat or a horse.

14. A method of controlling an ectoparasite infestation on a companion animal for a prolonged time, comprising orally administering a
15 formulation of Claim 1, 2, 3, 4, 5 or 6 to the animal

15. A long-acting, single-dose oral formulation of a spinosyn, or a physiologically acceptable derivative or salt thereof, for orally controlling an ectoparasite infestation on a companion animal for a prolonged time substantially as hereinbefore described with reference to any one of the Examples.

20

INDS02 NJH 325249

AMENDED CLAIMS

[received by the International Bureau on 29 December 2000 (29.12.00);
original claims 1, 3, 7, 8 and 11 amended; remaining claims unchanged (2 pages)]

CLAIMS

1. A single-dose oral formulation for controlling an ectoparasite infestation on a companion animal, said formulation comprising 0.1 to 75 percent by weight of a spinosyn, or a physiologically acceptable derivative or salt thereof, and a physiologically acceptable carrier, in an oral dosage form suitable for administration once every 7 days.
2. A formulation of Claim 1 wherein the spinosyn is spinosyn A.
3. A formulation of Claim 1 or 2 wherein the dosage form is a tablet, a liquid or a capsule.
4. A formulation of Claim 1 or 2 wherein the dosage form is an animal feed and the amount of the spinosyn comprises from 0.1 to 10 percent by weight of the feed.
5. A formulation of Claim 1, 2, 3 or 4 wherein the animal is a dog, a cat, a horse or a rabbit.
6. A formulation of Claim 1, 2, 3, 4 or 5 wherein the ectoparasite is a cat flea, a dog flea, a biting fly, a nuisance fly, a mosquito, a tick or a louse.
7. An article of manufacture, comprising packaging material and a formulation for controlling an ectoparasite infestation on a companion animal contained within said packaging material, wherein said formulation comprises
a unit dose of a formulation of Claim 1, 2, 3, 4, 5 or 6; and
wherein said packaging material comprises a label or package insert with instructions for orally administering the dose to the animal.

8. The use of a spinosyn, or a physiologically acceptable derivative or salt thereof, for the manufacture of a single-dose oral medicament for controlling an ectoparasite infestation on a companion animal comprising 0.1 to 75 percent by weight of a spinosyn suitable for administration once every 7 days.

9. A use of Claim 8 wherein the spinosyn is spinosyn A.

10. A use of Claim 8 or 9 wherein the animal is a dog, a cat, or a horse.

11. The use of a single-dose oral formulation of a spinosyn, or a physiologically acceptable derivative or salt thereof comprising 0.1 to 75 percent by weight of a spinosyn, for controlling an ectoparasite infestation on a companion animal suitable for administration once every 7 days.

12. A use of Claim 11 wherein the spinosyn is spinosyn A.

13. A use of Claim 11 or 12 wherein the animal is a dog, a cat or a horse.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/19557

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N43/22 A61K31/71 //(A01N43/22, 25:34, 25:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 375 316 A (LILLY CO ELI) 27 June 1990 (1990-06-27) page 3, line 8 - line 13 page 4, line 30 - page 5, line 12 page 17, line 50 - line 52 page 28, line 45 - line 47 page 40, line 53 - page 44, line 50 page 45, line 1 - line 7 page 45, line 49 page 45, line 51 page 45, line 52 - line 54 page 46, line 12 - line 20 page 46, line 23 - line 37 page 56, line 10 - line 25</p> <p style="text-align: center;">--- -/--</p>	1-15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

17 November 2000

Date of mailing of the international search report

30/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Lamers, W

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/19557

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 767 253 A (HUBER MARY L B ET AL) 16 June 1998 (1998-06-16) column 3, line 52 -column 5, line 11 column 23, line 20 -column 25, line 16 ---	1,3-8, 10,11, 13-15
A	DATABASE CROPU 'Online! D.P.RAINEY ET AL.: "The tissue distribution and metabolism of spinosyn A and D in lactating goats" retrieved from STN-INTERNATIONAL, accession no. 1996-85398 CROPU XP002153173 abstract & ABSTR. PAP. AM. CHEM. SOC. (211 MEET., PT. 1, AGRO045, 1996), -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/19557

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0375316	A	27-06-1990	AT 116325 T	15-01-1995
			AU 624458 B	11-06-1992
			AU 4689189 A	21-06-1990
			BG 60520 B	28-07-1995
			BR 1100144 A	28-03-2000
			BR 8906547 A	04-09-1990
			CA 2005784 A,C	19-06-1990
			CN 1043742 A,B	11-07-1990
			CZ 8907170 A	11-08-1999
			DD 290351 A	29-05-1991
			DE 68920301 D	09-02-1995
			DK 642089 A	20-06-1990
			EG 19191 A	29-09-1994
			ES 2065398 T	16-02-1995
			FI 95601 B	15-11-1995
			FI 96224 B	15-02-1996
			GR 3015598 T	30-06-1995
			HU 52562 A,B	28-07-1990
			IE 65919 B	29-11-1995
			IL 92743 A	21-10-1994
			IN 169756 A	21-12-1991
			JP 2223589 A	05-09-1990
			JP 2535080 B	18-09-1996
			KR 143566 B	15-07-1998
			MX 18755 A	31-01-1994
			NO 176914 B	13-03-1995
			NZ 231831 A	26-10-1994
			OA 9249 A	30-06-1992
			PT 92607 A,B	29-06-1990
			RO 106065 B	26-02-1993
			TR 26146 A	15-02-1995
			US 5496931 A	05-03-1996
			US 5571901 A	05-11-1996
			YU 239389 A	30-04-1991
			ZA 8909680 A	26-09-1990
			AU 631693 B	03-12-1992
			AU 6641490 A	31-05-1991
			BR 9006982 A	24-12-1991
			EP 0454820 A	06-11-1991
			JP 5504469 T	15-07-1993
			WO 9106552 A	16-05-1991
			US 5362634 A	08-11-1994
US 5767253	A	16-06-1998	US 5591606 A	07-01-1997
			US 5631155 A	20-05-1997